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A CLINICAL EVALUATION OF VERATRUM VIRIDE IN THE TREATMENT OF ESSENTIAL HYPERTENSION

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AS A therapeutic agent veratrum viride fell into disrepute many years ago. Formerly it was used to "soften the pulse" and lower the body temperature in infectious fevers. These effects were produced by administration of the drug in doses sufficient to cause collapse.[1] The tinctures in use at that time were so poorly standardized that the effective dose could not be calculated in advance. Because it slowed the pulse and lowered the blood pressure, often to a state of collapse, veratrum was thought to be a "cardiac depressant." For these various reasons the drug has been condemned in textbooks of pharmacology.[1-3] Actually, however, veratrum viride was cast into discard[3] before its pharmacologic effects on the circulatory system had been elucidated.[4]

A review of the more recent pharmacologic data concerning the veratrum alkaloids indicates that a significant reduction in arterial pressure occurs with doses below the toxic level.[5] The fall in arterial pressure apparently is associated with peripheral vasodilatation rather than with depression in cardiac output.[5,6]

Much pharmacologic evidence has accumulated to show that the circulatory effects of veratrum are mediated through nervous pathways. The reduction in blood pressure and cardiac rate observed with subtoxic doses in animals may be abolished by section or cold block of the vagus nerves.[5] Amann and Schaefer[7] have recently demonstrated that various afferent fibers are present in the cardiac branches of the vagus nerves which carry bursts of electrical activity in phase with the heart beat. These afferent nerves can be caused to fire off continuously by the injection of veratrine. Dawes[8] has confirmed in dogs and cats the fact that the reflex fall in blood pressure and heart rate following the injection of veratridine originates from the afferent vagus nerve endings in the myocardium of the left ventricle and in the lungs. This interesting laboratory evidence suggests that there is a vasodepressor mechanism mediated through the afferent vagus nerve endings in the thorax which can be excited to continuous activity by the veratrum alkaloids.

The effects of veratrum in the treatment of essential hypertension have not been extensively studied. Collins[9] observed the results of a single dose of

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the tincture in hypertensive patients. He concluded that definite and often striking reductions in blood pressure could occur with the use of subtoxic doses, but he made no attempt to treat his patients over long periods of time. The hypotensive effects were confirmed by Wedd[10] and by Hewlett and associates.[11] Hite[12] treated hypertensive patients continuously for eight months and concluded that veratrum viride is a valuable therapeutic agent in this disease. The drug has been used for many years in the treatment of eclampsia.[13-15] However, the available pharmacologic and clinical data suggested to us the need for re-evaluation of veratrum viride with particular reference to its use as a therapeutic agent in the treatment of essential hypertension. This communication reports the results of a clinical trial of this drug in a series of forty hypertensive patients. Experimental studies of the hemodynamic effects of veratrum, especially upon cardiac output, peripheral resistance, hepatic blood flow, renal clearances, sympathetic reflexes, limb and digit plethysmography, and skin temperatures will be reported elsewhere.[6]

SUBJECTS AND METHODS

The subjects were a heterogeneous group of forty patients with essential hypertension who were treated on the wards and in the Outpatient Department of the Massachusetts Memorial Hospitals. The period of observation under veratrum treatment varied from several weeks to as long as thirteen months. Thirty-one of the patients received the drug for periods longer than two months. Prior to treatment all patients were observed under routine symptomatic therapy including rest, sedation, and the usual forms of psychotherapy. Nine patients had previously received treatment with potassium thiocyanate and eight had received pentaquine.[16] Fifteen of the patients received treatment with a salt-free diet or the "rice diet." In all except the special instances described below, previous dietotherapy and drug therapy were withdrawn before veratrum was administered.

The blood pressure was measured with a mercury manometer with the patient in both the erect and the supine positions after he had rested for at least fifteen minutes in the supine position. The pulse rate was counted at the wrist or the cardiac apex.

The veratrum preparation used was the whole powdered mixture of alkaloids prepared in tablets. This preparation, which in our experience has had a fairly uniform potency, was biologically standardized so that each tablet contained 10 "Craw units."*

RESULTS

Therapeutic and Toxic Dosage.—The therapeutic dose of veratrum viride varied from 10 to 40 Craw units in those patients who responded to the drug. Increasing the dosage beyond this point resulted in further reduction of blood pressure, but inevitably led to toxic reactions. The margin between the therapeutic

*The preparation of veratrum viride which bears the trade name of "Vertavis" was generously supplied by Irwin, Neisler, and Co., Decatur, Ill. A Craw unit is defined as the amount which causes cardiac arrest in the crustacean, *Daphnia magna*.

and toxic doses usually was no greater than 10 Craw units. For any given individual the effective dose could be determined only by trial with gradually increasing doses. The therapeutic dose bore no relation to the surface area of the patient or the severity and duration of the disease.

If the effective dose was greater than 10 Craw units, ingestion of the total dose at one time frequently resulted in side reactions, particularly nausea and vomiting. However, by subdividing the total effective dose so that no more than 10 Craw units were administered at hourly intervals, these side reactions were reduced considerably.

Time-Dose Relationships.—Although there was great individual variation in the size of the effective dose (herein defined as that dose which resulted in a reduction of at least 20 mm. in systolic and 15 mm. in diastolic blood pressure), the onset and duration of the hypotensive response was quite uniform in different patients. When an effective dose was administered, the hypotensive response began in one or two hours, reached a maximum in four to six hours, and ended in approximately twelve to fourteen hours. An example of this sequence is provided by a patient admitted to the hospital because of hypertensive crisis with encephalopathy.

CASE 1.—J. Mc., a 51-year-old white man, was admitted to the Evans Memorial Hospital on June 16, 1947. On the day of admission he was seen in the outpatient department where he was found to be mentally confused. The blood pressure, which had previously been 240/130, had risen to 270/170. In the hospital he was observed to be disoriented as to time and place; he exhibited echolalia, mixed visual and verbal agnosia, and acoustic agnosia. Neurological examination revealed no localizing signs. Venesection was performed with the removal of 500 ml. of blood without significant reduction of blood pressure.

Veratrum viride was then administered in amounts of 10 Craw units every hour for three doses followed by 10 Craw units every other hour for three doses (Fig. 1). Eight hours after veratrum was begun, the blood pressure had fallen to 150/60, and the pulse rate, from 125 to 80 per minute. Eight hours after veratrum had been discontinued, the blood pressure began to rise again, stabilizing at 230/140 sixteen hours after the last dose of the drug. The pulse rate rose to 100 per minute. During the period of hypotension there was gradual clearing of the sensorium so that twenty-four hours after admission the patient was oriented as to time and place and was able to carry on an intelligent conversation.

If the dosage intervals were not separated by at least eight hours, successive doses soon resulted in the appearance of toxic reactions. The toxic effects resulting from cumulative overdosage may be illustrated by the following case.

CASE 2.—L. S., a 39-year-old white woman, with known hypertension for eight years, complained of dyspnea, orthopnea, and dependent edema for five months prior to admission to the hospital. After two weeks of hospital treatment with digitalis and mercurial diuretics, the signs of cardiac failure cleared. The blood pressure at this time was 210/135. Treatment with veratrum was begun and the dosage was gradually increased to 90 Craw units per day administered in divided doses of 30 Craw units at 10:00 A.M., 2:00 P.M., and 6:00 P.M. At 6:30 P.M. the patient experienced numbness in the feet, hands, and lips, blurred vision, increased sweating, soon followed by nausea with severe vomiting, excess salivation, and collapse in the upright position. The blood pressure at this time was 120/80 and the pulse rate, 54 (Fig. 2). These symptoms gradually abated during the next three hours and had completely disappeared in sixteen hours.

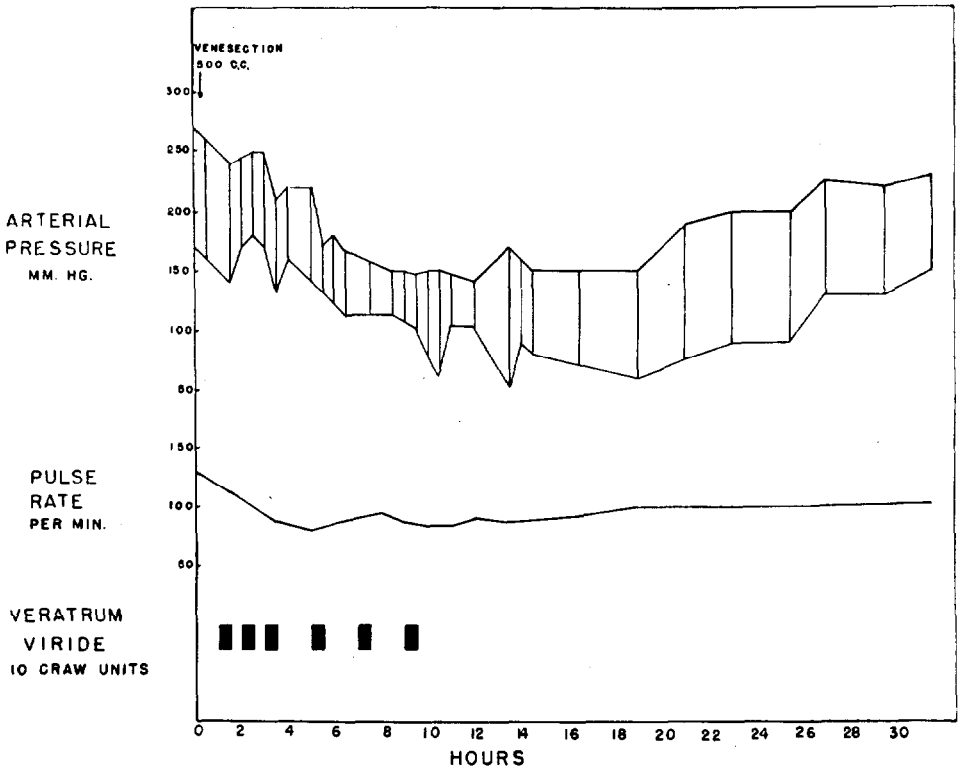

Fig. 1.—The duration of the hypotensive response to orally administered veratrum viride as shown in Patient J. Mc. (Case 1).

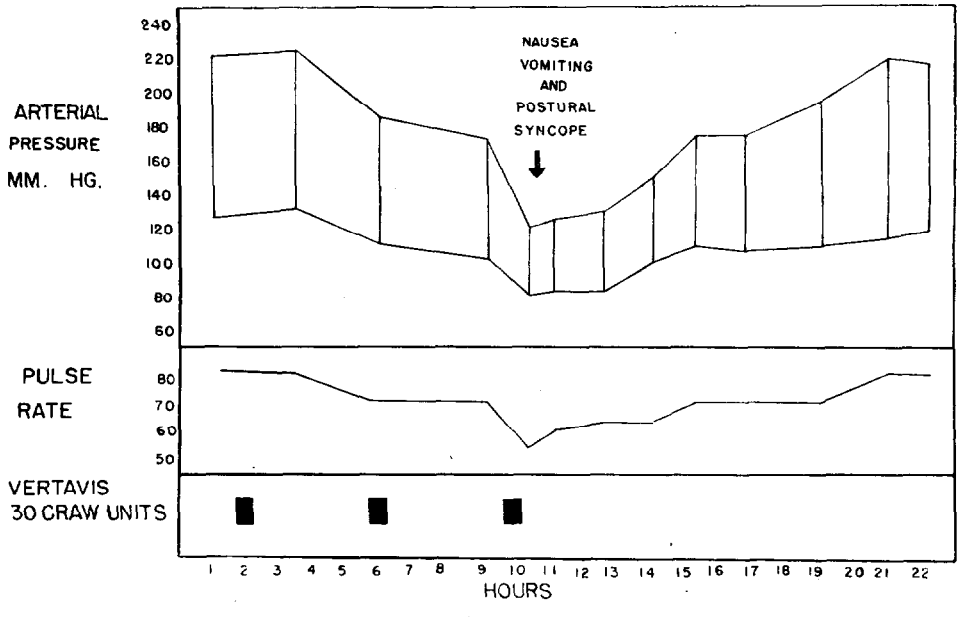

Fig. 2.—The toxic reaction resulting from the effects of cumulative overdosage when veratrum was administered at intervals of four hours (Case 2).

This patient received three doses of 30 Craw units at four-hour intervals. Since veratrum is present and active in the body for twelve hours, at 6:30 P. M. she suffered the toxic reactions resulting from a cumulative dose of 90 Craw units. Such severe reactions were fairly frequent in the early phase of the investigation, but were almost completely eliminated when the effective doses were separated by a twelve-hour interval.

Therapeutic Results.—

Hospitalized Cases: In order to evaluate the hypotensive activity of veratrum viride under controlled conditions, the drug was administered to six hospitalized patients who had shown little hypotensive response to other types of medical treatment, including hospital bed rest (Table I). During the control period three patients received sedation in the form of phenobarbital (30 mg. three times per day), two patients received the Kempner rice diet[17] for ten days and two weeks, respectively, and one patient was given a "salt-free" diet supplemented with mercupurin (2.0 c.c. intravenously twice per week). The period of control observations in the hospital varied from ten to thirty days prior to the institution of veratrum treatment.

In each case all blood pressures were recorded by the same individual. The blood pressure taken initially was not recorded and the patient was then allowed to rest for thirty minutes. Following this initial period, the blood pressure and pulse rate were recorded once a minute for five minutes in the supine position, followed immediately by five minutes in the erect position, and then a final five minutes in the supine position. In the control period the lowest values for systolic pressure, diastolic pressure, and pulse rate were selected to compare with the highest values recorded in the period after treatment with veratrum viride.

Although all of these patients were hospitalized throughout the study, they were not in bed at all times, except four patients whose blood pressures were recorded after forty-eight hours or more of complete rest in bed. In every case, after treatment with veratrum was begun, patients were allowed to be up and about the ward. The previous regimen of treatment was continued, the only change being the addition of veratrum viride.

The results listed in Table I indicate that in five of the six cases a significant reduction in blood pressure occurred following therapeutic doses of veratrum viride. In one case (Patient L. S.) significant hypotension did not occur after therapeutic doses, but developed only after toxic doses. In the four cases in which the drug was withdrawn, there was a prompt return of blood pressure to pretreatment levels.

Outpatient Cases: The foregoing results seemed sufficiently significant to warrant further clinical trial of veratrum viride over longer periods of time in ambulatory patients. The latter data are summarized in Table II. Of the thirty-four patients studied, all except four exhibited a significant reduction in blood pressure when compared with the values obtained during the control period. However, the results were seldom as striking as after acute administration of the drug in the hospital, and in only one case did the blood pressure fall to normal.

TABLE I. THE HYPOTENSIVE EFFECT OF VERATRUM VIRIDE COMPARED WITH THAT OF OTHER FORMS OF THERAPY IN HOSPITALIZED PATIENTS

PATIENT	SEX	AGE (YEARS)	KNOWN DURATION OF HYPERTENSION (YEARS)	TIME AFTER ADMISSION TO HOSPITAL (DAYS)	TREATMENT	BLOOD PRESSURE		PULSE RATE PER MINUTE
						LYING	STANDING	
C. S.	M	43	10	1	0	234/160	253/172	90
				3	Complete bed rest 48 hrs.	232/146	233/160	85
				10	0	225/130	210/150	92
				12	Vertavis, 30 Craw units b.i.d.	190/110	190/130	68
				15	Vertavis discontinued	225/130	222/154	84
R. Mc.	M	38	1	1	0	190/140	185/140	72
				14	Low-salt diet; mercurials	170/135	170/140	68
				16	Vertavis, 10 Craw units daily	142/100	120/90	58
M. S.	F	48	6	1	0	218/140	215/152	75
				3	Complete bed rest 48 hrs.	210/130	220/145	75
				30	Strict rice diet 10 days	190/130	190/150	82
				34	Vertavis, 40 Craw units, single dose	155/105	160/130	90
				43	Vertavis discontinued	220/138	215/144	82
				48	Vertavis, 30 Craw units b.i.d.	175/115	180/125	80

L. S.	F	43	8	1	0	218/160	225/160	115
				14	Phenobarbital, 30 mg. t.i.d.	215/120	210/140	80
				18	Vertavis, 90 Craw units (over 8-hr. period)	150/80*		64
				20	0	220/120	210/135	82
				21	Vertavis, 40 Craw units b.i.d.	200/120	200/120	84
C. B.	M	43	2	1	0	220/140	240/160	85
				3	Complete bed rest 48 hrs.	232/145	222/158	82
				10	Phenobarbital, 30 mg. t.i.d.	240/140	230/155	80
				14	Vertavis, 30 Craw units b.i.d.	195/130	160/130	60
				24	Vertavis discontinued	220/130	230/150	82
P. P.	M	41	5	1	0	240/145	235/160	70
				4	Complete bed rest 72 hrs.	235/140	215/160	65
				18	Strict rice diet 2 weeks	240/162	208/170	76
				23	Vertavis, 30 Craw units b.i.d.	180/135	146/126	62
				27	Vertavis discontinued 24 hrs.	230/138	220/155	74
				33	Vertavis, 30 Craw units b.i.d.	146/96	130/104	50

*Collapse, nausea, and vomiting.

Except for the periods of complete bed rest noted, the patients were up and about the ward. Prior to veratrum, different types of medical therapy were substituted as indicated. When treatment with veratrum was started, the immediately preceding medical therapy was continued and was maintained even after veratrum was discontinued.

TABLE II. RESULTS OF THERAPY WITH VERATRUM VIRIDE IN THIRTY-FOUR AMBULATORY HYPERTENSIVE PATIENTS TREATED FOR PERIODS OF 1 TO 13 MONTHS

PATIENT	SEX	AGE	KNOWN DURATION OF HYPERTENSION (YEARS)	CONTROL PERIOD						AFTER VERATRUM VIRIDE						
				DURATION OF OBSERVATION (MONTHS)	NUMBER OF VISITS	MEAN OF BLOOD PRESSURE RECORDINGS—MM. HG		MEAN PULSE RATE SUPINE PER MINUTE	CRAW UNITS PER DAY	DURATION OF OBSERVATION (MONTHS)	NUMBER OF VISITS	MEAN OF BLOOD PRESSURE RECORDINGS—MM. HG		MEAN PULSE RATE SUPINE PER MINUTE	TOXIC REACTIONS	SYMPTOMATIC IMPROVEMENT
						SUPINE	ERECT					SUPINE	ERECT			
C. B.	F	52	10	2 weeks*	14	235/140	220/140	76	50	13	46	200/125	165/110	78	0	++
R. Mc.	M	38	1	2 weeks*	28	170/140	170/140	60	30	10	12	160/100	150/110	54	0	+++
C. S.	M	45	8	2 weeks*	14	225/140	225/145	80	60	12	14	210/125	205/125	68	+	+++
G. P.	M	48	7	12	6	190/120	190/125	95	50	13	18	170/110	155/110	68	0	++
P. E.	F	44	13	1	3	220/135	200/140	80	60	4	9	170/100	145/110	76	+	+++
J. F.	M	56	2	1	3	240/100	210/105	82	80	6	8	200/85	170/95	64	+	0
V. F.	F	36	13	8	6	255/150	265/170	108	80	2	5	245/160	245/160	103	0	+
C. F.	M	52	1	4	7	210/120	210/120	76	60	9	20	180/105	170/110	76	0	++
R. K.	M	52	10	1	3	200/115	210/135	72	30	2	4	180/100	160/100	68	0	0
J. Mc.	M	66	6	2	4	240/145	235/150	104	50	6	9	210/130	190/130	90	0	+++
I. S.	M	46	6	2 weeks*	60	170/110	180/130	84	70	2	4	150/110	150/120	76	0	+
E. S.	F	50	21	2	4	240/140	195/150	84	70	6	14	210/120	180/120	72	+	+
E. A.	F	54	4	3 days*	10	240/150	220/160	100	50	10	12	225/130	210/140	90	0	++
N. F.	M	34	0	6	5	170/125	155/125	72	40	2	4	150/100	140/110	65	+	+

F. G.	F	45	28	3	4	255/120		78	30	6	8	240/115		70	0	+++
P. H.	F	47	0.2	1	4	230/130	180/130	76	30	3	4	180/100	160/110	0	+	++
J. C.	M	51	0.3	10	20	210/145	180/140	68	40	2	6	195/125	160/115	68	+	+
J. D.	M	38	7	2	4	180/120	160/130	88	40	2	5	160/105	160/105	82	0	0
E. S.	F	45	0	1 week*	24	225/140	190/130	90	60	2	4	185/120	170/115	54	0	+++
I. P.	M	30	6	3	4	160/120	170/130	80	50	3	3	145/95	135/110	76	0	+
J. S.	M	57	6	7	4	170/90	160/90	74	40	1	3	135/75	145/85	70	0	0
A. C.	M	45	0.5	6	8	180/110	170/100		70	1	3	145/90	140/90	72	0	+++
M. C.	F	42	6	8	5	185/120		84	20	4	5	160/90		84	0	+++
C. D.	F	43	1	6	10	215/130	195/125	92	50	2	6	185/120	170/125	94	0	++
W. G.	M	49	2	1	4	190/130	190/140	100	50	4	4	170/110	180/130	80	0	+++
M. A.	M	41	7	1 week*	7	170/115	165/120	110	50	10	12	170/120	170/120	94	0	++
L. Mc.	F	51	12	12	6	215/110	210/120	65	30	3	8	165/95	150/100	58	+	0
F. D.	M	30	0.6	4 weeks*	28	180/120		76	60	2	10	130/85	125/90	70	+	+
M. A.	M	41	7	5	8	210/130	200/140	80	60	4	6	190/130	170/120	80	+	+
N. C.	M	54	0.4	3	6	190/110	180/120	90	40	4	8	190/110	140/100	68	+	+++
L. B.	F	46	5	1	4	190/115	210/120	80	60	3	10	185/120	165/115	72	+	+
E. H.	F	57	0.5	2	4	190/115	180/120	112	50	1	4	165/105	133/110	120	0	++
W. B.	M	46	0.5	1	3	200/115	190/120	80	30	1	2	155/105	160/110	76	0	+
M. D.	M	43	2	3	5	180/120	175/125	76	50	2	4	150/95	155/105	64	+	+

*Observations made in the hospital.

Twenty-seven of the thirty-four patients (79 per cent) expressed subjective improvement. Three patients felt worse while taking the drug, and the remaining four patients either had no complaints prior to or during treatment or noted no change in their symptoms. The most remarkable improvement occurred in those patients who complained of exertional dyspnea and palpitation. Many patients noted a general improvement in physical and mental well-being which often was associated with a definite hypotensive response.

In several of the patients who had been taking veratrum for periods longer than one month, reductions in the cardiac silhouette by roentgenography as well as changes toward normal in the electrocardiogram were demonstrated (Figs. 3 and 5). There was no evidence of change in renal function as measured by concentration tests, routine urinalysis, and the excretion of phenolsulfonphthalein.

Following treatment with veratrum viride, a remarkable dilatation of the retinal arterioles has been reported in a patient with eclampsia.[18] A similar relaxation of arteriolar spasm was occasionally observed in the optic fundi in this series of patients with essential hypertension. In one patient, in whom there was generalized constriction of all the branches of the ophthalmic artery with numerous local spasms in the nasal branches, the caliber of the vessels reverted entirely to normal during the period of hypotension. Such marked changes were seen only in those patients who exhibited great reductions in blood pressure.

The most interesting results with veratrum were obtained in the so-called "resistant" types of cases. Patients with high diastolic and/or wide pulse pressure, those with long-standing hypertension, and those with cardiac failure or repeated cerebrovascular accidents responded as well as the early mild cases. Sex and age did not materially alter the response to the drug. A number of the patients in this series, although far from cured, were able to return to work from a life of semi-invalidism. The following cases serve as illustrative examples:

CASE 3.—C. S., a 45-year-old white man, had a history of two cerebrovascular accidents in the fifteen months prior to admission to the hospital. On the advice of his physician he retired from his work as manager of a bakery. In the hospital he was found to have cardiac enlargement, Grade III arteriosclerotic and Grade II hypertensive changes in the eye grounds, and impaired renal function without nitrogen retention. After two weeks of rest in the hospital, during which time he received a salt-free diet, the blood pressure was 240/130.

Treatment was begun with veratrum and the dosage was increased to 30 Craw units every twelve hours. The blood pressure fell immediately to 190/110. He was discharged from the hospital feeling considerably improved and within a month had returned to work. During the past eight months his blood pressure was never higher than 210/120 on repeated outpatient visits and usually was well below this figure.

He was readmitted to the hospital for further study seven months after beginning treatment with veratrum. Re-examination of the heart by roentgenography revealed diminution in cardiac size. The electrocardiogram showed changes toward normal since the examination seven months previously (Fig. 3).

After the second hospital day the medication was discontinued for fifty-four hours. It will be noted in Fig. 4 that soon after the medication was withdrawn the blood pressure gradually rose from a general level of 185/110 to a level of 230/120. With the resuming of veratrum therapy the blood pressure returned to the lower level. It is of interest that when the drug was discontinued the patient complained of headache and palpitation which again disappeared after treatment was resumed.

The following case demonstrates the effect of veratrum in a patient with cardiac failure secondary to hypertension.

CASE 4.—R. Mc., a 38-year-old resort hotel manager, noted the onset of exertional dyspnea, substernal oppression, and occasional attacks of paroxysmal nocturnal dyspnea eight months prior to admission to the hospital. Five months before admission he consulted his physician who found his blood pressure to be 220/140. He was advised to stop work and was given digitoxin, 0.2 mg. per day, nitroglycerin, and occasional injections of mercurial diuretics. He failed to improve, however, and was admitted to the hospital.

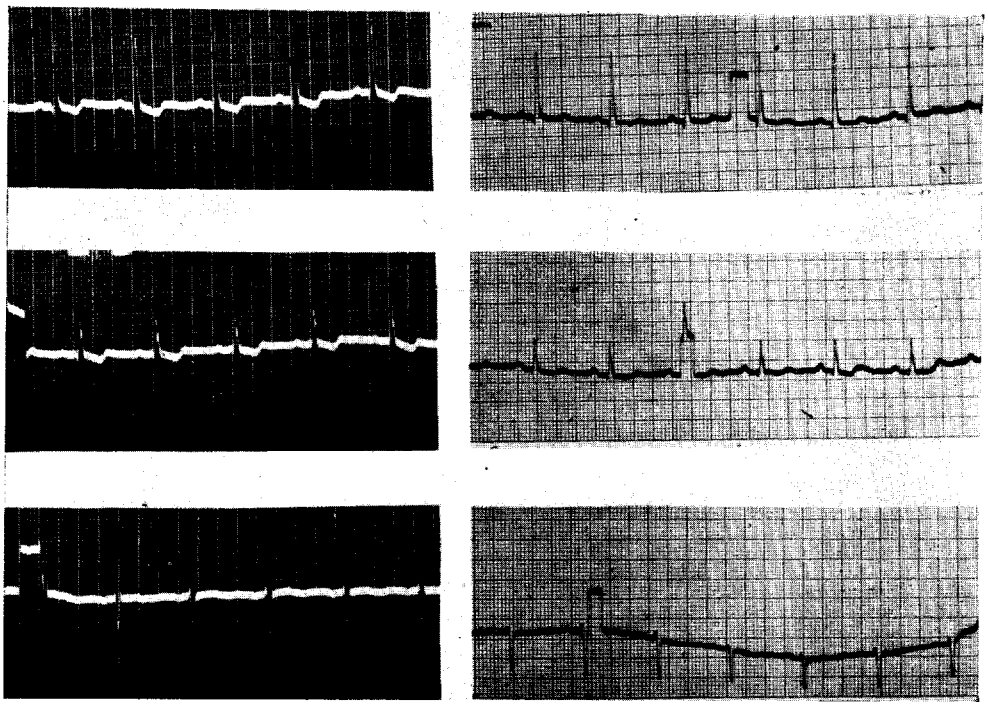

Fig. 3.—Electrocardiograms of Patient C. S. (Case 3). The three limb leads are shown from above downward. The electrocardiographic tracing on the left was taken prior to treatment and that on the right was taken after seven months of continuous treatment with veratrum viride. Inverted T waves in Leads I and II have now become upright.

Physical examination revealed the signs of cardiac failure including edema of the lower extremities. There was narrowing and tortuosity of the retinal arterioles. The urine contained 3 plus albumin and concentrated to 1.018. Phenolsulfonphthalein excretion was reduced. The electrocardiogram was interpreted as showing digitalis effects and left ventricular strain. There was cardiac enlargement and pulmonary congestion by roentgen ray.

The blood pressure, which was 190/140 on admission, fell to 170/120 several days after admission. The edema of the legs cleared after diuresis with mercupurin. Veratrum therapy was begun at a dosage level of 10 Craw units twice per day. The blood pressure in the supine position fell to 140/100, and in the standing position, to 120/90. He was discharged from the hospital on this dosage plus digitoxin 0.2 mg. daily, and in two months returned to work.

During the past seven months since discharge, the blood pressure ranged between 180/110 in the supine and 160/110 in the erect position. He experienced no further attacks of dyspnea or angina and has required no further treatment with either mercurial diuretics or nitroglycerin.

Roentgenographic examination of the heart six months after veratrum was begun showed reduction in cardiac size and clearing of congestive changes (Fig. 5). It was necessary gradually to increase the dosage of veratrum to 30 Craw units every twelve hours in order to maintain the hypotensive response. The patient was employed through a strenuous summer season with no evidence of cardiac failure. On one occasion veratrum was withdrawn for a period of five days. This was followed by a rise in blood pressure from 180/110 to 210/130 and an increase in pulse rate from 64 to 100 per minute. During this period the patient noted palpitation which promptly disappeared as soon as the drug was resumed.

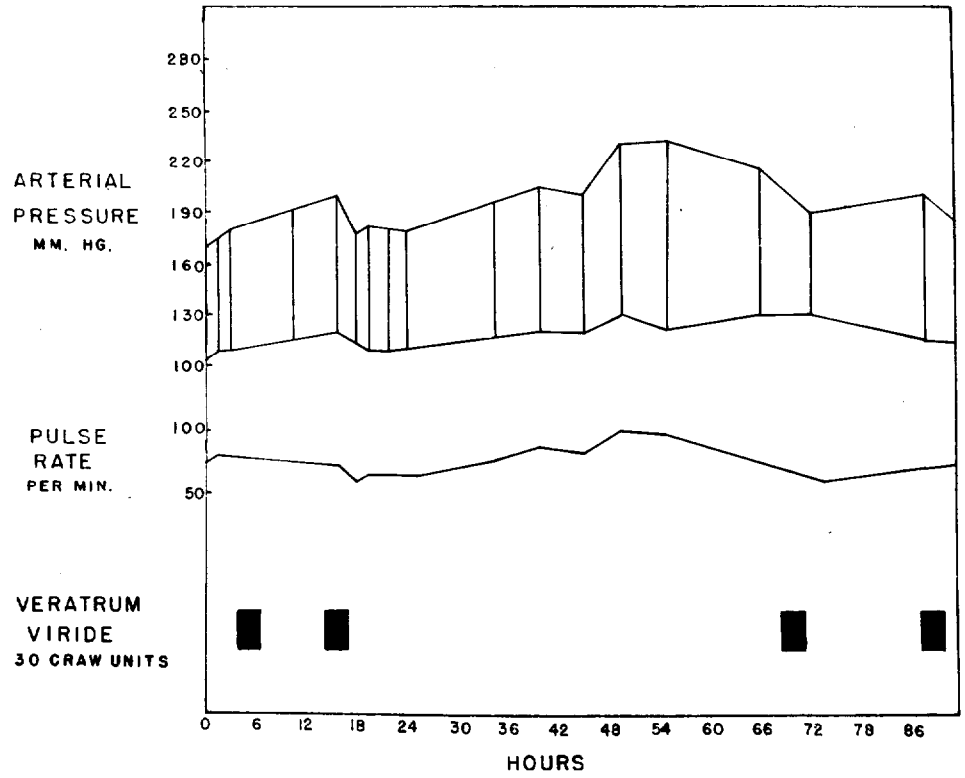

Fig. 4.—The effect of withdrawing medication in Patient C. S. (Case 3) who had been treated with veratrum viride continuously for seven months. Withdrawal of the drug was followed by elevation of the blood pressure and pulse rate which again fell following reinstitution of treatment.

Veratrum viride was also found to enhance the effectiveness of sympathectomy and of dietotherapy. The following case illustrates the effect of veratrum in a patient maintained on a low-salt diet.

CASE 5.—C. F., a 52-year-old white man, a shoe worker, suffered from headaches and dizzy spells for six months prior to his first visit to the outpatient department. Examination revealed the blood pressure to be 220/120, the heart to be slightly enlarged with no signs of failure, the retinal arteries to be narrowed and sclerotic, and renal function to be unimpaired, with no albuminuria and good concentrating ability.

Treatment with potassium thiocyanate was begun, but despite a blood level of 9 to 11 mg. per cent, maintained for one and one-half months, there was no reduction in the blood pressure and the patient complained of increased dizziness. Potassium thiocyanate was discontinued and

a low-salt diet instituted, salt-free milk powder* and salt-free bread being used. After one month on this regimen the blood pressure fell to 190/110 and the symptoms of headache and dizziness were relieved.

After the blood pressure had been stabilized at 190/110 on repeated clinic visits, veratrum was administered, the diet being continued meanwhile, and the dosage was gradually increased to 30 Craw units every twelve hours. One week after this dosage was attained the blood pressure was 160/100, fluctuating between this value and 175/110 during the next three months. When veratrum was withdrawn the blood pressure rose again to 190/110, promptly falling to 160/100 when the drug was readministered.

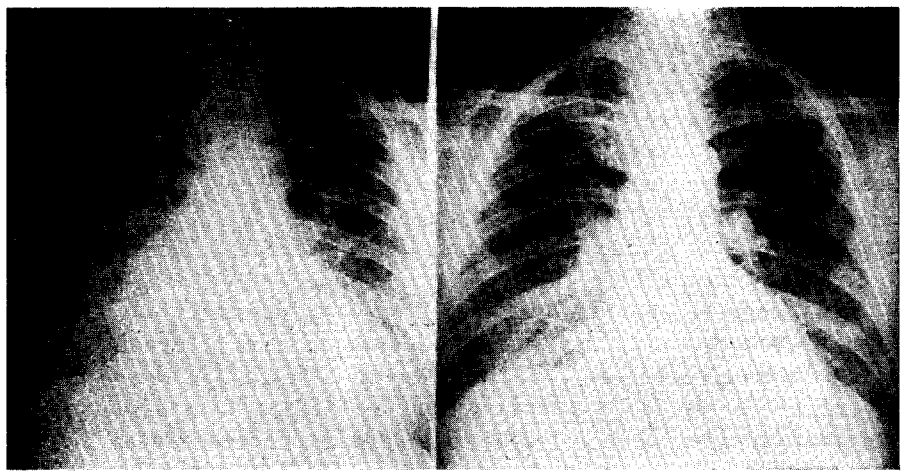

Fig. 5.—The reduction in cardiac size and clearing of pulmonary congestive changes in Patient R. Mc. (Case 4). The roentgenogram on the left was taken prior to treatment and that on the right was taken after seven months of continuous treatment with veratrum viride.

Toxic Reactions and Side Effects.—The reaction to a toxic dose of veratrum viride was in many ways similar to vasovagal collapse.[19] The pulse rate was slowed to between 45 and 60 beats per minute; the blood pressure was markedly reduced, and on one occasion fell to shock levels; there was sweating, nausea, repeated vomiting, salivation, collapse in the erect position, blurring of vision, mental confusion, and a sense of numbness in the extremities and around the mouth.† The bradycardia, but not the hypotension, was relieved by doses of 1.0 mg. of atropine sulfate administered intravenously. The hypotension could be abolished with ephedrine. These toxic reactions, although alarming to the patient, passed off in about five hours, leaving no residua. Such severe effects although largely avoided since the drug has been administered at intervals of eight hours or more, were sufficiently frequent to require careful and frequent observation of all patients under treatment.

Milder side effects occurred, such as nausea, transient blurring of vision, and a sensation of numbness, particularly about the mouth. In some cases, these effects appeared with and in some, before the hypotensive effects, necessitating

*Generously supplied under the name of "Lanolac" by the Mead Johnson Co., Evansville, Ind.

†Such a severe collapse, particularly when associated with a substernal burning sensation, may be mistaken for a coronary occlusion.

the discontinuation of treatment. Occasional attacks of nausea, although not uncommon, were seldom sufficient to cause withdrawal of the medication, but frequently necessitated readjustment of dosage.

The most frequent side effect was a sensation of epigastric burning occurring soon after the ingestion of each dose. This effect was not entirely due to local gastric irritation[1] since similar symptoms were observed following parenteral administration of veratrum viride.

Drug Tolerance.—The phenomenon of tachyphylaxis following the administration of veratrum in animals has been well documented.[5] Tachyphylaxis, apparently, is much less likely to occur with minimal effective doses than with large doses.[4,20] Clinically, in hypertensive patients the development of some degree of drug tolerance was occasionally observed. However, tolerance seldom became complete so that a considerable reduction in blood pressure could still be obtained at the end of twelve or more months of treatment. The typical dramatic result of short-term treatment has been described in Case 1, while the usual less marked hypotensive effect obtained after long-term therapy has been illustrated in Case 3. Occasional patients required less rather than more medication after long-continued treatment.

With continued administration of the drug at a constant dose level it was not unusual to note the sudden or gradual development of nausea and vomiting after days, weeks, or months. Following several such episodes these side effects passed off or in some cases persisted requiring a wider spacing or actual reduction in dosage. The possibility of combatting these developments with the use of tablets containing 5 rather than 10 Craw units, or tablets with enteric coatings, and/or by the use of atropine or hyoscine is under investigation at present.

Adjustment of Dosage.—Since the effective and toxic doses were quite variable in different patients, successful therapy depended upon gradually increasing the dosage in each case and necessitated repeated observations, especially during the early phases of treatment. The following methods of administering the drug were found to be most efficacious. The patient was given an initial dose of 10 Craw units after the morning and evening meals. Outpatients were seen in the clinic after several days of medication, the visit being so arranged that the blood pressure and pulse rate were recorded approximately four to six hours after the patient had received his last medication. Provided that neither a definite hypotensive response nor toxic reactions had occurred, the dosage was increased to 20 Craw units morning and evening administered in subdivided doses of 10 Craw units at hourly intervals, preferably separated by a meal. By such repeated observations of blood pressure, pulse rate, and symptoms, the dosage was increased gradually until a therapeutic effect or toxic reaction occurred.

In hospitalized patients a similar procedure was adapted, or the following more rapid method was used. The rapid method consisted in administering the drug in amounts of 10 Craw units at intervals of two hours while recording the blood pressure and pulse rate responses every half hour until a therapeutic or toxic effect occurred. Minor readjustments of dosage frequently were necessary after the patient had left the hospital.

DISCUSSION

The results of this investigation indicate that veratrum viride is useful in the treatment of certain cases of essential hypertension. The dramatic hypotensive response following short-term administration established the efficacy of the drug in the treatment of so-called "hypertensive crisis." In this condition veratrum was far more effective in our hands than the customary therapeutic methods of venesection or heavy sedation. In addition, the less dramatic but nevertheless significant and prolonged hypotensive effects of veratrum in several severely hypertensive patients, including some with cardiac failure, warrants the hope that such patients may receive lasting benefit from this therapy.

In less severe cases of hypertension, therapy with veratrum was not as useful as in the severe cases. Careful attention to dosage and frequent readjustment of dosage were necessary because of side effects and the development of drug tolerance. Therefore, the milder forms of essential hypertension were more effectively treated by diet, reassurance, sedation, and rest, and, in selected cases, by lumbodorsal splanchnicectomy

However, cases of long-standing hypertension with marked elevations of blood pressure, not benefitted significantly either by diet or surgery, and more or less incapacitated by the disease, were compensated for the occasional toxic reactions to veratrum by the relief afforded from the symptoms of the disease. In such cases the combined use of a salt-free diet and veratrum viride proved to be more efficacious than either therapeutic agent used alone.

SUMMARY AND CONCLUSIONS

1. Veratrum viride in the form of the whole powdered mixture of alkaloids was administered orally to a series of forty patients with essential hypertension for periods up to thirteen months.

2. When the drug was administered by the oral route, the hypotensive effect began to appear at the end of one or two hours, reached a maximum in four or six hours, and largely disappeared by the end of fourteen hours. In order to obtain maximum therapeutic benefit and to avoid toxic reactions resulting from cumulative overdosage, veratrum was administered at dosage intervals of twelve hours. In addition, in order to provide greater therapeutic safety, this dosage interval was further subdivided so that no more than 10 Craw units were ingested per hour. The great variability of response to a given dose in different individuals required the gradual increase of dosage in each patient in order to avoid toxic side effects.

3. Veratrum was found to be a useful therapeutic agent in the treatment of patients with (a) "hypertensive crisis," (b) severe, long-standing hypertensive disease which proved resistant to other forms of treatment, and (c) hypertension complicated by cardiac failure.

4. Prolonged therapy in some cases resulted in a diminution in cardiac size and reversal of electrocardiographic changes toward normal.

5. There were no deaths and no toxic reactions resulting in more than transient disability attributable to the drug. However, the development of

side effects and of changing sensitivity to a given dose were sufficiently frequent to limit its usefulness in the treatment of patients with mild or moderate degrees of hypertension.

6. Veratrum viride appeared to have therapeutic value as an adjunct to dietotherapy and to the routine treatment of hypertensive heart disease.

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REFERENCES

1. Sollman, T.: A Manual of Pharmacology, ed. 5, Philadelphia, 1937, W. B. Saunders Company, p. 538.
2. Goodman, L., and Gilman, A.: The Pharmacological Basis of Medical Therapeutics, New York, 1941, The Macmillan Company, p. 575.
3. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, ed. 2, Philadelphia, 1901. Lea and Brothers, p. 335.
4. Cramer, W.: On the Action of Veratrum Viride With Some Remarks on the Interrelationship of the Medullary Centres, J. Pharmacol. & Exper. Therap. **7**:63, 1915.
5. Krayer, O., and Acheson, G. H.: The Pharmacology of the Veratrum Alkaloids, Physiol. Rev. **26**:383, 1946.
6. Freis, E. D., Stanton, J. R., Culbertson, J. W., Halperin, M. H., Litter, J., and Wilkins, R. W.: Unpublished data.
7. Amann, A., and Schaefer, H.: Ueber Sensible Impulse im Herznerven, Pflüger's Arch. f. d. ges. Physiol. **246**:757, 1943.
8. Dawes, G. S.: Studies on Veratrum Alkaloids. VII. Receptor Areas in the Coronary Arteries and Elsewhere as Revealed by the Use of Veratridine, J. Pharmacol. & Exper. Therap. **89**:325, 1947.
9. Collins, R. J.: The Clinical Actions of Veratrum, Arch. Int. Med. **16**:54, 1915.
10. Wedd, A. M.: Veratrum Viride in Auricular Fibrillation, Heart **12**:307, 1925.
11. Hewlett, A. W.: The Pulse Flow in the Brachial Artery. V. The Influence of Certain Drugs, Arch. Int. Med. **20**:1, 1917.
12. Hite, W. K.: Hypertension and Veratrum Viride, A Preliminary Study, Illinois M. J. **90**:336, 1946.
13. Haultain, F. W. N.: Notes on Some Cases of Eclampsia Treated With Veratrone, Edinburgh M. J. **11**:313, 1913.
14. Bryant, R. D., and Fleming, J. G.: Veratrum Viride in the Treatment of Eclampsia, J. A. M. A. **115**:1333, 1940.
15. Irving, F. C.: The Treatment of Eclampsia and Pre-Eclampsia With Veratrum Veride and Magnesium Sulfate, Am. J. Obst. & Gynec. **54**:731, 1947.
16. Freis, E. D., and Wilkins, R. W.: Effect of Pentaquine in Patients With Hypertension, Proc. Soc. Exper. Biol. & Med. **64**:455, 1947.
17. Kempner, W.: Compensation of Renal Metabolic Dysfunction. Treatment of Kidney Disease and Hypertensive Vascular Disease With Rice Diet, North Carolina M. J. **6**:61,117, 1945.
18. Willson, J. R., and Smith, R. G.: The Peripheral Circulatory Action of Veratrum Viride, J. Pharmacol. & Exper. Therap. **79**:208, 1943.
19. Lewis, T.: Diseases of the Heart, ed. 4, London, 1946, The Macmillan Company, Ltd., p. 110.
20. Krayer, O., Wood, E. H., and Montes, G.: Studies on Veratrum Alkaloids. IV. The Sites of the Heart Rate Lowering Action of Veratridine, J. Pharmacol. & Exper. Therap. **79**:215, 1943.